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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No.: 40

Application Number: 08/470,489
Filing Date: 06/06/95
Appellants: Montagnier, L., *et al.*

Rebecca M. McNeill
For Appellant

SUPPLEMENTAL EXAMINER'S ANSWER

Pursuant to the Remand under 37 C.F.R. § 1.193(b)(1) by the Board of Patent Appeals and Interferences on 17 December, 2001, a Supplemental Examiner's Answer is set forth below.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellants' statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellants' brief includes a statement that claims 90-109 do not stand or fall together and provides reasons as set forth in 37 C.F.R. § 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9)Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

(10) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims: Claims 90-109 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The claims are directed toward methods of detecting HIV-2 nucleic acids employing HIV-2 specific probes that are capable of hybridizing to said nucleic acids under the recited melting temperatures (e.g., 42°C, 20°C, or 3°C) or methods of preparing said probes. The broadest claim (claim 90) simply stipulates that the probe comprises HIV-2 nucleic acids that hybridize to HIV-2_{ROD} genomic DNA at the recited melting temperatures. Other limitations specify that the probe comprises any HIV-2 nucleic acid molecule obtained

from particular regions of any HIV-2 genome (e.g., nucleotides (nt) 1-380 of the U3/R region of the LTR; nt 1-1566 of the *gag* gene; nt 1114-1524 or the *gag* gene; nt 1-405 of the *gag* gene; nt 406-1155 of the *gag* gene; or nt 1-2673 of the *env* gene). Finally, additional limitations state that the probes are obtained from nucleic acids encoding different HIV-2_{ROD} proteins. Thus, the claims potentially encompass nucleic acids of varying lengths (i.e., 10 nt, 20 nt, 50 nt, 100 nt, 1000 nt, etc.) derived from any HIV-2 isolate or genomic region. The probes employed are not directed toward any specific nucleotide sequence or any particular length.

The disclosure describes the isolation and preliminary characterization of a novel human immunodeficiency virus type 2 (HIV-2) isolate designated ROD (HIV-2_{ROD}). Detailed nucleotide sequence data was provided from subgenomic HIV-2_{ROD} clones corresponding to the U3/R region (nt 1-380) of the long terminal repeat (LTR) (see Figs. 6 and 7), the *gag* gene (nt 1-1521; see pp. 56 and 57), and the *env* gene (nt 1-2628; see pp. 58-61). Hybridization studies were carried out to assess the genetic relatedness of ROD to other retroviral isolates (e.g., HIV-1 or SIV). Stringent (e.g., 50% formamide, 0.1% SDS, 5X SSC, at 42°C) or non-stringent (e.g., 30% formamide, 0.1% SDS, 5X SSC, at 42°C) hybridization reaction conditions are described for this analysis. Various HIV-1 nucleic acid probes were used in this study (pBT1, endonuclease, protease, pRS3 (envelope)). Specific HIV-2 probes were **not** described or discussed in this portion of the disclosure (pp. 17-22). A specific HIV-2_{ROD} probe (E2/pSPE2) is described that corresponds to the U3/R LTR region (380 nt) on page 24. This probe was employed as a full-length probe. Probes corresponding to specific fragments of this nucleotide sequence were **not** described. This probe was employed to screen a recombinant phage library and

a full-length proviral genomic HIV-2_{ROD} clone was identified. Fragments of this full-length clone (pROD 27-5, 35-3, 4.6, 4.7, and 4.8) were subcloned into other cloning vectors. Generic statements are made (pp. 49-50) specifying that the invention encompasses DNAs or DNA fragments, especially from the *env* and *pol* regions, that share various homologies to the parent sequence (e.g., 50%, 70%, 90%). It was further stated that "equivalent" DNAs that hybridize under "non-stringent" conditions are also encompassed. Page 53 of the specification discusses utilizing probes that are derived from the subgenomic cloned inserts, or fragments thereof. It was again stated that said probes were to be employed under "non-stringent" hybridization parameters. Finally, specific cDNA fragments are described pertaining to nt 1-405, 406-1,155, and 1,156-2,574 of the ROD *gag* gene, as well as, nt 1-2,574 of the ROD *env* gene. No other fragments or subgenomic probes are identified.

The disclosure does **not** describe the identification and preparation of specific HIV-2_{ROD}, or probes from any other HIV-2 isolate, of defined sequence or length with the exception of those particular sub-genomic clones clearly identified in the specification. The disclosure also **fails** to describe any particular fragments that were prepared from these sub-genomic clones. Furthermore, the disclosure does **not** describe the identification and preparation of a single HIV-2 probe, obtained from the isolate ROD or any other HIV-2 isolate, that was based upon the recited melting temperatures. It is well-known in the art that the melting temperature (T_m) of any given duplex is simply defined as the temperature when half of the nucleic acid duplex molecules have dissociated into their constitutive single strands. It is affected by several parameters including the monovalent cation concentration (M, in moles per liter), the base composition

expressed as the molar fraction of G and C residues, the length of the shortest nucleotide strand in the duplex (L), and the concentration of helix-destabilizing agents such as formamide. For mismatched probes, the T_m decreases depending upon the degree of mismatch. Factors affecting the hybridization rate and stability of the double-stranded nucleic acid also include the temperature, cation concentration, percentage of base mismatch, probe strand length, solvent, pH, and base composition. Thus, merely reciting limitations vis-à-vis the T_m fails to provide any significant structural guidance pertaining to the actual probe employed. Without providing a reference sequence, the skilled artisan would be left to guess the characteristics of the corresponding probe. Simply reciting a T_m does not lead the skilled artisan to any particular nucleotide sequence. Moreover, the disclosure does **not** describe the identification, preparation, and purification of a single probe based upon the T_m. This is nothing more than a wish by applicants to capture subject matter that was neither contemplated by them or in their possession at the time of filing.

Furthermore, additional legal precedence clearly dictates that conception of a chemical compound (e.g., a DNA molecule) is not achieved until reduction to practice has occurred (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q.2d 1016 (C.A.F.C. 1991); *Fiers v. Revel*, 25 U.S.P.Q.2d 1601 (C.A.F.C. 1993); *In re Bell*, 26 U.S.P.Q.2d 1529 (C.A.F.C. 1993); *In re Deuel*, 34 U.S.P.Q.2d 1210 (C.A.F.C. 1995); *University of California* v. *Eli Lilly*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997); *Enzo Biochem, Inc.* v. *Gen-Probe, Inc.*, 63 U.S.P.Q.2d 1609 (C.A.F.C. 2002)). In *Amgen, Inc.*, the court ruled that:

> Conception of chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than

> simply defining it solely by its principal biological property; thus, when inventor of gene, which is chemical compound albeit complex one, is unable to envision detailed constitution of gene so as to distinguish it from other materials, as well as method for obtaining it, conception is not achieved until reduction to practice has occurred, and until after gene has been isolated.

The court in *Eli Lilly* further elaborated on this point and concluded that:

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers* v. *Revel.*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

The significance of conception and reduction to practice was further addressed by the court in *Fiers* where it was emphasized that:

> Conception is question of law, reviewed de novo on appeal, and if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated; thus, regardless of complexity or simplicity of method of isolation employed, conception of DNA sequence, like conception of any chemical substance, requires definition of that substance other than by its functional utility.

Finally, the court noted in *Enzo Biochem* that the written description requirement can be met "by showing that an invention is complete by disclosure of sufficiently detailed, relevant

identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Thus, it appears that adequate written support for a large genus of nucleic acids requires significant structural information.

In the instant application, applicants have identified a single HIV-2_{ROD} full-length proviral genomic clone and a small number of HIV-2_{ROD} sub-genomic clones. Preliminary characterization of the clones was performed by subjecting them to restriction mapping and limited nucleotide sequence analysis. However, **the disclosure does not provide detailed structural information for any given HIV-2_{ROD} probe, or a probe derived from any other HIV-2 isolate, with respect to any given Tm.** Thus, the skilled cannot readily envisage or ascertain the nucleotide sequence of any given HIV-2 probe that is required for the claimed methodologies. Since the claimed nucleic acid probes are defined solely in terms of functional language (i.e., having a certain Tm), these limitations clearly fail to impart any further defining structural criteria to said nucleic acids. It is readily manifest that applicants are attempting to claim nucleic acid probes that were never contemplated nor possessed by applicants.

(11) Response to Argument

Appellants traverse and submit they are claiming methods, not compositions, as the Examiner purportedly argues. Appellants also assert that the case law relied upon is inapposite. Appellants obviously fail to understand or appreciate that the claimed methodologies cannot be practiced without specific HIV-2 probes.

Moreover, the probes must have a specific T_m. In order to reliably detect HIV-2 retroviral nucleic acids in any given biological sample, the skilled artisan would require a well-defined and characterized probe. In order to assess the T_m of any given probe, the skilled artisan would also need to know the isolate, genomic region, and nucleotide sequence of the probe. As previously set forth, the disclosure fails to set forth any particular probes based upon the T_m. This information is simply not provided. Moreover, the case law relied upon is clearly germane since the methods claimed require the specific probes. Without these reagents, none of the methodologies can be practiced. Thus, appellants' arguments are clearly specious.

Appellants further argue that the specification provides specific sequences and hybridization conditions that will work. First, the disclosure does not describe the identification, preparation, and purification of a single HIV-2-specific probe based vis-à-vis the T_m of any given duplex. Appellants are clearly attempting to capture subject matter that was neither conceived nor possessed at the time of filing. Second, as set forth *supra*, it has been noted that the disclosure provided describes the preparation of a single full-length proviral HIV-2_{ROD} genomic clone and sub-genomic clones obtained from this isolate. Appropriately drafted claim language directed toward these reagents would be acceptable (i.e., detection methods employing the insert of pSPE2 as a suitable probe). However, the disclosure fails to describe the identification, preparation, and purification of a single HIV-2-specific nucleic acid probe based upon the T_m.

Appellants additionally argue that the disclosure provides specific hybridization parameters. It should be noted that none of the parameters employed appear in the claim language. It should also be noted that the mere recitation of hybridization parameters

does not provide any additional guidance pertaining to the actual nucleotide sequence of any given probe. As previously set forth, several parameters affect duplex formation including inter alia the length of the probe, G/C content of the probe, monovalent cation concentration, and solvent concentration. The fact that a hybridization reaction may be carried out under certain conditions, in the absence of a reference isolate, does not provide any guidance pertaining to the nucleotide sequence of the actual probe employed. Furthermore, the hybridization parameters described in the specification were in reference to the utilization of the pSPE2 insert under low-stringency. Low-stringent hybridization reaction conditions often suffer from a number of limitations such as high background noise due to non-specific hybridization. Thus, a reliable detection method requires a highly specific reagent. This clearly is not provided by the claims.

Appellants additionally argue that the Office has failed to provide an explanation as to why the claimed methodologies fail to receive adequate written support. This argument is clearly untenable in view of prior Office actions and section 10 above. Thus, the skilled artisan, upon perusal of the disclosure, would reasonably conclude that appellants were not in possession of the claimed invention at the time of filing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Examiner, Art Unit 1648

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Supervisory Patent Examiner, Art Unit 1648

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08 January, 2004

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